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COVID-19 in the Perioperative Setting: A Review of the Literature and the Clinical Landscape

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Abbreviations: ARDS—acute respiratory distress syndrome; APSF—Anesthesia Patient Safety Foundation; ASA—American Society of Anesthesiologists; ASA PS—American Society of Anesthesiologists Physical Status; ASC—ambulatory surgery center; ECMO—extracorporeal membrane oxygenation; NNV—number needed to vaccinate; PASC—Post-Acute Sequelae of SARS-CoV-2; PEM—post-exertional malaise; PICS—post-intensive care syndrome; POTS—postural orthostatic tachycardia syndrome; PPE—personal protective equipment; PTSD—post-traumatic stress disorder; RCRI—revised cardiac risk index; VTE—venous thromboembolism

Abstract:

The COVID-19 pandemic has dramatically affected societies and healthcare systems around the globe. The perioperative care continuum has also been under significant strain due to the pandemic—tasked with simultaneously addressing surgical strains and backlogs, infection prevention strategies, and emerging data regarding significantly higher perioperative risk for COVID-19 patients and survivors. Many uncertainties persist regarding the perioperative risk, assessment, and management of COVID-19 survivors—and the energy to catch up on surgical backlogs must be tempered with strategies to continue to mitigate COVID-19 related perioperative risk. Here, we review the available data for COVID-19-related perioperative risk, discuss areas of persistent uncertainty, and empower the perioperative teams to pursue evidence-based strategies for high quality, patient-centered, team-based care as we enter the third year of the COVID-19 pandemic.

Introduction:

The last two years of the COVID-19 pandemic have left an indelible mark on populations around the globe, and the healthcare system is irreparably changed. The pandemic has dramatically impacted healthcare delivery including increased national healthcare spending, supply chain disruptions, delayed routine and preventive healthcare services, strained inpatient and outpatient healthcare system capacity, and loss of healthcare workforce. The availability of new knowledge, and articulated areas of uncertainty, remains fast-paced and humbling. We are still only beginning to glimpse the long-term effects of prior infection with SARS-CoV-2 (COVID-19), Long COVID, and potential disability amongst COVID-19 survivors.

The perioperative setting bears no exception to these concerns. The impact of the global pandemic on the surgical space quickly extended beyond the onus on surgical cancellations in the early months of the pandemic. We now have steadily mounting data on the impact of SARS-CoV-2 infection on perioperative risk and the impact across the perioperative and surgical space. With global COVID-19 cases approaching half a billion and with approximately 300 million surgeries performed worldwide annually,[1, 2] we estimate hundreds to thousands of COVID-19 survivors will present for surgical care in the near future. Here, we aim to summarize the available perioperative literature published during these two years and articulate clinical unknowns and areas of uncertainty.

Clinical Risk:

Our early awareness of the potential perioperative impact of infection with SARS-CoV-2 (COVID-19) began in early 2020. Early case reports and case series were published from China, Iran, and Italy—countries with the earliest surges. These reports demonstrated surgical risk dramatically higher than population averages, with associated acute respiratory distress syndrome (ARDS), cardiac injury, cardiopulmonary arrest, multiorgan injury, and mortality.[3-6] Much of this patient-level data was observed before the potential for asymptomatic infection with COVID-19 was recognized and months before standard preoperative COVID-19 screening protocols were implemented. These cases also demonstrated the potential for rapid acute clinical deterioration of patients who had entered operating rooms either with an asymptomatic infection or during the incubation period or who contracted COVID-19 postoperatively.[4, 6, 7]

By April 2020, institutions began developing preoperative screening for asymptomatic COVID-19 infections. This was a strategy for infection prevention and personal protective equipment (PPE) preservation, especially once we learned about the potential for asymptomatic infection and contagiousness. That month, the American Society of Anesthesiologists (ASA) and Anesthesia Patient Safety Foundation (APSF) issued perioperative testing guidelines.[8] Currently, preoperative testing protocols remain in place. With the recent dramatic increase in the availability of at-home COVID-19 rapid antigen testing across the United States, the

question of how to incorporate home test results into the perioperative setting has grown.[9] A sweeping review of preoperative testing policies, including the sensitivity and specificity of available forms of COVID-19 testing, is beyond the scope of this review.

In addition to infection prevention, the onus on preoperative testing for COVID-19 expanded to risk mitigation for patients. The first larger studies on this patient population were published in late Spring 2020. The COVIDSurg international, multi-center retrospective cohort study of 1128 patients demonstrated dramatically higher mortality and pulmonary complication rates than baseline (23.8% and 51.2%, respectively).[10] Independent risk factors for complications included male gender, age > 70yo, American Society of Anesthesiologists Physical Status (ASA PS) Class 3-5, malignancy, and emergency or major surgery. Elevated mortality and pulmonary complications were also seen for younger, healthy patients having minor or non-emergent surgeries. Doglietto et al.'s matched cohort study from Italy also demonstrated significantly higher mortality, pulmonary complication, and venous thromboembolism (VTE) rates (OR 9.5, 4.98, and 13.2, respectively).[11]

In March 2021, the COVIDSurg group published the first large, prospective study on perioperative COVID-19 risk.[12] Both symptomatic recovered and asymptomatic patients had elevated risk, with pulmonary and mortality risk lasting for seven weeks. The risk persisted longer than seven weeks for patients with residual symptoms. Risk factors for complications included male sex, age ≥ 70 , ASA class 3-5, Revised Cardiac Risk Index (RCRI) score ≥ 1 , surgery for malignancy, emergency surgery, and major surgery.

Interval studies continue to demonstrate elevated postoperative risk persisting for at least four weeks from index infection, including mortality, pulmonary complications, or VTE risk.[13-19] This elevated risk of postoperative complications is also seen with postoperative acquisition of COVID-19 infection.[4, 6, 20, 21]

Mechanism of perioperative risk and areas of uncertainty

Studies indicate that any recent respiratory illness can increase perioperative risk, and this variable is included in the ARISCAT pulmonary complication risk calculator.[22] However, COVID-19 is more than a "common cold." Current understanding of the pathophysiology of COVID-19, especially severe infection, permits us to conceptualize the mechanism for significant rates of postoperative complications. COVID-19 is a pro-inflammatory and prothrombotic state associated with cytokine production and endothelial dysfunction.[23, 24] Similar pathophysiology contributes to cardiovascular, neurocognitive, and other postoperative complications in the absence of COVID-19. The potential for synergy between COVID pathophysiology and the heightened inflammatory state of the perioperative period could be the driving mechanism for increased perioperative complications in post-COVID-19 patients, but explicit mechanistic studies are needed.

There are several areas of clinical uncertainty regarding perioperative COVID-19 risk that must be considered. While most available data has been focused on pulmonary complications, VTE, and mortality, other concerning perioperative COVID-19 complications, including organ damage, are not as well-described (Table 1). For example, acute kidney injury is a common manifestation of patients hospitalized with COVID,[25] and was found to be increased in COVID patients undergoing urgent and emergent surgical procedures compared to non-COVID surgical patients.[26]

Perioperative COVID-19-related cardiac data is needed. Aside from cardiac complications in the early case reports of perioperative COVID[3, 5], larger-scale studies have not examined cardiac complications. COVID-19 is associated with multiple cardiac complications, including myocarditis, cardiomyopathy, and arrhythmias.[27, 28] Cardiac complications are also reported in patients asymptomatic at the time of index COVID-19 infection.[27] The preoperative assessment must consider the potential for COVID cardiac complications, especially for patients with new or residual cardiopulmonary symptoms or a decline in functional status.[29, 30] Also, we are unaware of any perioperative data regarding outcomes and best practices for COVID-19 survivors who required extracorporeal membrane oxygenation (ECMO).

Neurocognitive dysfunction and damage after COVID infection are also common.[31-36] Delirium is a well-recognized complication of COVID and is associated with a poor prognosis and increased mortality. While specific post-COVID perioperative neurocognitive complications are not yet reported, we remain highly concerned about the risk of postoperative delirium and other postoperative neurocognitive disorders. Emerging research regarding perioperative brain health may intimately intersect with the perioperative post-COVID spectrum of care.[37] Perioperative teams should also be aware of the potential for cognitive dysfunction and neuropsychiatric manifestations of prolonged hospitalization and/or critical illness due to the index infection (ex. Post-intensive care syndrome [PICS], post-traumatic stress disorder [PTSD], sleep derangements).

Beyond organ dysfunction, COVID-19 has the potential to contribute to preoperative frailty, decreased exercise tolerance, sarcopenia, and deconditioning related to the index infection or post-COVID-19 complications.[38-40] Jonker et al. demonstrated that COVID-recovered patients who survived perioperative COVID-19-related complications were more likely than non-COVID-19 patients to remain hospitalized or be discharged to rehabilitation.[14] Perioperative teams should consider the potential for frailty and deconditioning related COVID-19 complications and whether there is an opportunity to optimize perioperative prehabilitation or rehabilitation.

Perioperative outcomes data for patients with Long COVID or Post-Acute Sequelae of SARS-CoV-2 (PASC), the syndrome of persistent or new symptoms following infection with COVID-19 (Table 2),[41-43] is lacking. The emerging knowledge regarding the manifestations and pathophysiology of Long COVID informs the

perioperative space, raising concern for postural orthostatic tachycardia syndrome (POTS), orthostasis, post-exertional malaise (PEM), other cardiopulmonary complications, and neuropsychiatric manifestations.[44]

Data regarding the perioperative risk for vaccinated patients with breakthrough infections is also lacking. The concern for risk above baseline persists as COVIDsurg (3/2021) demonstrated elevated risk in asymptomatic patients.[12] Contemporary data are anticipated from COVIDsurg-3.[45] An additional topic for further investigation is whether different COVID variants are associated with differential perioperative risk. For example, does the concept that “omicron is a milder disease” extend to the perioperative space?

Based on current evidence, the perioperative risk is higher in major versus minor surgeries. However, the March 2021 COVIDsurg study excluded procedures “typically performed outside of the operating theatre” or those performed by “non-surgeons,” even those procedures performed with anesthesiology (including interventional gastroenterology, cardiology, radiology).[12] Since data from the operating room might not be generalizable to other procedures, institutions should use caution when extrapolating existing evidence to the periprocedural realm to determine the interval from deisolation and resolution of symptoms to scheduling an elective procedure.

Available guidelines

In December 2020, the ASA/APSF issued a joint statement regarding time-based criteria for proceeding with elective surgery based on the severity of the index COVID-19 infection and patient characteristics.[46] This was updated in February 2022,[9] shifting to a seven-week waiting interval before elective surgery. The ASA/APSF reported insufficient evidence to determine the appropriate length of time between post-vaccination infection and surgery.[47] Also, in February 2022, the joint statement from the Association of Anaesthetists, Royal College of Surgeons of England, and other English societies used stronger language regarding a seven-week wait time, including for vaccinated patients and patients suspected to have an omicron infection.[48]

Both society statements acknowledge that many surgeries are time-sensitive and cannot wait seven weeks from the index COVID-19 infection. Risk/benefit discussions for time-sensitive surgeries in COVID survivors remain a significant challenge, complicated by the fact that time-sensitive surgeries are often emergency or malignancy-related surgeries, both of which are independent risk factors for worse postoperative outcomes.[10, 12, 17] We recommend multidisciplinary planning and risk counseling discussions, including shared-decision making with patients. We also strongly recommend that perioperative COVID-19 is not overlooked in favor of catching up on large surgical backlogs.

Risk mitigation and risk assessment

As noted above, studies have shown that certain patient characteristics (i.e., age, sex, infection severity) are independent risk factors for worse postoperative outcomes. However, even younger, healthier patients have an increased risk of postoperative complications until at least seven weeks post-infection.[10] Two risk calculators have been proposed[49, 50], but neither incorporates time since index infection or other variables such as biomarkers.

Biomarkers have been examined as prognostic factors for COVID-19 infection. Examples include inflammatory markers or acute phase reactants (D-dimer[51, 52], ferritin,[53] c-reactive protein[54]), other labs (leukopenia or lymphopenia,[55] thrombocytopenia[55, 56], acute kidney injury, liver injury[57]), and cardiac biomarkers (high-sensitivity troponin, nt-pro-BNP/BNP)[54, 58, 59]. Although perioperative data is limited, there may be a role for incorporating biomarkers into perioperative risk assessments and prognoses.

Another area for investigation is the role of how approved COVID-19 therapeutics affect or mitigate perioperative risk. Patients hospitalized for COVID-19 might have received remdesivir, an antiviral drug, or other therapeutics, including dexamethasone. While guidance regarding monoclonal antibodies has changed with the omicron surge,[60, 61] the FDA recently authorized two oral antivirals (nirmatrelvir/ritonavir, molnupiravir) as an outpatient treatment option for COVID-19 in specific patients.[62, 63] If a patient received an approved therapy, the information should be incorporated into their preoperative history to guide clinical assessment and determine the risk of drug-drug or drug-anesthetic interactions. Ritonavir, in particular, is a potent CYP3A4 inhibitor, leading to interactions with numerous perioperative agents.[64] Similarly, any use of non-approved therapy (ivermectin, etc.) should be queried, especially as these may increase perioperative risk through known adverse effects or interaction with anesthetic agents, analgesics, or sedatives.[65]

An additional research question is whether the type of anesthesia has a role in mitigating post-COVID-19 surgical patients' perioperative risk. For example, one study showed no impact on mortality risk between regional or general anesthesia for patients with proximal femur fractures,[20] and case reports regarding the role of regional anesthesia are emerging.[66] Another area for future investigation is optimizing care for post-COVID-19 patients in an ambulatory (non-hospital) setting. Early data showed that patients having minor procedures are also at increased risk[10, 67]. Ambulatory surgery centers (ASC) will continue to have increasing COVID-19-recovered and Long COVID patients. An understanding of prognostic factors may aid in future venue triage protocols.[68]

Finally, there is little evidence to guide postoperative risk mitigation strategies. While increased VTE risk is recognized,[14, 18] we have no consensus guidelines for prevention or treatment.[69] In the meantime, evidence-informed strategies for any patient at high risk for VTE can be extrapolated to the post-COVID-19 patient. Perioperative teams should consider VTE risk based on the surgery and patient history to guide

therapeutic and prophylactic-dose anticoagulation decisions. Patients on preoperative anticoagulation therapy should resume treatment postoperatively as soon as possible.

Available protocols and assessment pathways

Protocols recommending intervals between COVID-19 infection and surgery must address 1) waiting time from index infection, 2) subjective patient assessment, and 3) objective patient assessment. Granular, patient-centered history and physical examination is the hallmark of preoperative assessment. A COVID-19 survivor should be asked detailed questions about the nature and course of their infection, including date of symptom onset and positive testing, residual or new symptoms, treatments received, vaccination status, and pre- and post-infection functional/exercise capacity. To our knowledge, our institutional protocol was among the first published framework for evaluating post-COVID-19 surgical patients.[29] Various (inter)national societies have issued recommended intervals between COVID-19 infection and surgery and have acknowledged that a more nuanced preoperative evaluation and risk assessment should be performed.[46, 70, 71]

Onus on vaccinations

When COVID-19 vaccinations became available to the general public in the United States in early 2021, new perioperative questions and challenges arose. The safety of COVID-19 vaccination close to the time of surgery was queried, and the minimum waiting time between vaccination and surgery remains unclear. Theoretical concerns included decreased vaccine immunogenicity, increased postoperative complications, and potential for confusion in assessing postoperative complications (ex. fever). However, adult perioperative data has demonstrated that these concerns are not supported by the literature (i.e., seasonal influenza vaccination).[72, 73] Data demonstrated that the number needed to vaccinate (NNV) to lower overall infection-related mortality is lower in the perioperative population than in the general population.[74] The Society for Thoracic Surgery recommends that patients complete the vaccination series before elective surgery, ideally at least two weeks before surgery to achieve full vaccination status, but allowing at least a few days between vaccination and surgery date.[75] The European society joint statement also recommends that the complete vaccination series, including appropriate boosters/third doses, be received at least two weeks preoperatively. They suggest that vaccination confirmation and counseling should optimally occur at the time of surgery decision-making.[48]

Ethical questions remain regarding vaccination requirements before elective surgery; vaccination requirements for transplant surgeries are already standard.[76] Additionally, with the backlog of surgical cases, questions remain about whether vaccinated patients should be prioritized over unvaccinated patients.

Conclusion

The impact of COVID-19 on the perioperative care continuum extends far beyond individual patient risk. During the last two years, the ongoing surgical strain has been difficult to measure and articulate, but it has

been immense and is anticipated to persist for the foreseeable future. This strain extends far beyond the loss of surgical revenue to hospitals and surgeons. Estimates of lost surgical case volume globally are well within the eight digits.[77, 78] Patients have been harmed—whether or not they had COVID-19-infection—due to the strain on the surgical system and other pandemic-related societal changes.[79, 80] Ongoing challenges to the perioperative team include moral injury and the impact of ethical conundrums, including resource allocation, loss of healthcare workforce, worsening of gender inequity, and detrimental effects to training programs.[81-84]

In summary, the perioperative space has had a front-row seat to the pandemic. While we are starting to understand the perioperative risk related to SARS-CoV-2 infection (COVID-19), many areas of uncertainty remain and represent unique questions for perioperative research investigations. Despite the knowledge gaps, this patient population presents opportunities for evidence-based, patient-centered, multidisciplinary team-based care—especially grounded at the institutional level with support from society guidelines. We eagerly await more data about this clinical challenge that impacts a large volume of our perioperative patients and the broader perioperative space.

Declaration of interests

- ☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
- ☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

<u>Organ System Affected by COVID-19</u>	<u>Potential Perioperative Complications</u>
Generalized	Frailty Deconditioning Malnutrition Sarcopenia Decreased exercise tolerance Post-exertional malaise
Neurocognitive Neuropsychiatric	Delirium Postoperative cognitive dysfunction Sleep abnormalities Post-intensive care syndrome Cerebrovascular disease Autonomic instability or autonomic neuropathy Other neuropathies
Pulmonary	Chronic restrictive lung disease Chronic hypoxic respiratory failure Acute respiratory distress Upper airway injury related to intubation
Cardiac	Cardiomyopathy Myocarditis Ischemic heart disease Arrhythmias Postural orthostatic tachycardia syndrome
Renal	Post-infection CKD including dialysis Acute kidney injury 25, 26
Hematologic	Venous thromboembolism Thrombocytopenia Disseminated intravascular coagulation
Endocrine	Autoimmune thyroid disease New onset diabetes mellitus
Gastrointestinal	Liver function test abnormalities

Table 1: perioperative concerns and considerations based on the risk of organ damage due to SARS-CoV-2 (table created by the authors)

<u>National Institute of Health (USA) (39)</u>	<u>Centers for Disease Control (USA)(41)</u>	<u>World Health Organization (40)</u>
Wide range and/or constellation of symptoms reflecting lack of recovery “a few weeks” after COVID-19 index infection	Wide range of new, returning, or ongoing symptoms after COVID-19 infection, occurring at least four weeks after COVID-19 infection	Symptoms occurring in an individual with confirmed or suspected COVID-19, usually three months from the onset of COVID-19 infection and lasting at least two months, and which cannot be explained by an alternative diagnosis

Table 2: comparison of currently available definitions of Long COVID or Post-Acute Sequelae of SARS-CoV-2 (PASC)

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